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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,439	08/01/2005	Anita Mehta	RLL-267US	3824

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/525,439	MEHTA ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15-19,21,22,24,25,27-29,31,32,34,35,51 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5* is/are allowed.

6)☒ Claim(s) *1-3,7-9,15,17 and 27* is/are rejected.

7)☒ Claim(s) *4,6,10,11,16,18,19,21,22,24,25,28,29,31,32,34,35,51 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/1/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 15-19, 21, 22, 24, 25, 27-29, 31, 32, 34, 35, 51 & 53 are currently pending in the instant application; of which **Claims 1-10, 15-17, 27, 29, 31, 32, 34, 51 & 53** have been amended. **Claims 12-14, 20, 23, 26, 30, 33, 36-50, 52 & 54** have been cancelled.

Priority

This application is a 371 of PCT/IB02/03433, filed on August 23, 2002. No claim for priority is presented.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on August 1, 2005 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Specification

The abstract of the disclosure is objected to because it is not completely legible. The bottom part of the WO document submitted has been cut off. Please submit a clear copy.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-9 & 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein **Ar = aryl; X = no atom; and Y = $(CH_2)_q$, wherein q = 0,** does not reasonably provide enablement for compounds wherein **Ar = heteroaryl; X = oxygen, sulphur, or nitrogen; and/or Y = CHR_5CO or $(CH_2)_q$, wherein q = 1-4.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) *The breadth of the claims;*
(B) *The nature of the invention;*
(C) *The state of the prior art;*
(D) *The level of one of ordinary skill;*
(E) *The level of predictability in the art;*

(F) *The amount of direction provided by the inventor;*
(G) *The existence of working examples; and*
(H) *The quantity of experimentation needed to make or use the invention based on the content of the disclosure.*

The breadth of the claims - The nature of the invention

Claims 1-3, 7-9 & 17 are drawn to compounds according to formulae I, II, III, and IV, wherein the definitions of **R_1, R_2, R_4, R_6, R_7, Z, Q, W, X and Y** are defined therein. Compounds according to these formulae are potentially useful as pharmaceuticals.

The state of the prior art

The Examiner notes that upon review of a comprehensive search encompassing the formulae I, II, III, and IV, including all core variables, there is no prior art exists that would anticipate or render the compounds obvious. Therefore, there is nothing in the art that shows how to make and use all of the compounds as claimed in the instant application, so the Examiner must be guidance (support) in the specification in order to enable one of skill in the art to make and use this invention as claimed.

The level of predictability in the art

A functional group or elemental substitution changes the necessary starting materials for making these compounds as well as the reactivity of said starting materials. For example, changing an aryl to heteroaryl (**R_2**) is a non-obvious change; and accordingly is the change from a bond to a heteroatom or alkyl chain (**X-Y**). Said changes in functional groups or elements influence several properties of the compound, such as bond length, electronegativity, and therefore the localization of electrons with respect to the core functionality. Therefore, it is unpredictable to know, from the

outlined examples in the instant specification, how to make *all* of the compounds as claimed in formulae I, II, III, and IV.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to make the claimed compounds commensurate in the scope with the instant claims. There is a lack of information pertaining to the synthesis of any compound according to formulae I, II, III, and IV, except for when **Ar = aryl, X = a bond, and Y = $(CH_2)_q$, wherein q = 1-4.**

The existence of working examples

The working examples set forth in the instant specification are directed to the compounds of formulae I, II, III, and IV, in which **Ar = aryl, X = a bond, and Y = $(CH_2)_q$, wherein q = 1-4**. There has not been provided sufficient evidence that would warrant the skilled artisan to accept the synthetic examples provided in the specification as correlative proof that any compound of formulae I, II, III, and IV, would indeed be able to be synthesized using the methods as outlined.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation of any compound of formulae I, II, III, and IV, wherein **Ar, X, and Y** are as defined. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. One skilled in the art

would be confronted with an undue burden of experimentation to acquire alternative starting materials in view of formulae I, II, III, and IV AND attempt to prepare the desired products with no guarantee of success. Furthermore, one skilled in the art would be confronted with an undue burden of experimentation to isolate, characterize, and test the various compounds of formulae I, II, III, and IV.

Claims 1, 7, 17 & 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of the formulae I, II, III and IV; including enantiomers, diastereomers, N-oxides and pharmaceutically acceptable salts thereof; the specification is not enabled for *solvates, esters, polymorphs, prodrugs or metabolites* thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Nature of the Invention

The nature of the invention is the compounds of formulae I, II, III and IV, and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The state of the prior art and the predictability or lack thereof in the art

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug

product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization, (Morissette *et al.* Advanced Drug Delivery Reviews **2004**, *56*, 275-300).

For instance, the phenomenon of polymorphism, in the crystallization of organic compounds, is of crucial importance to the pharmaceutical industry. Two polymorphs of the same drug molecule may have different physical properties: e.g. solubility,

bioavailability, melting points, density, hardness, or color; and may have dramatically different properties that effect the scale-up process. Due to the differences between polymorphs, the drug regulatory authorities (e.g. the FDA) are increasingly demanding more information about potential drug products before granting approval. The conditions under which polymorphs interconvert is also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling, compression, and storage. Therefore, for these reasons, the state of the prior art is one of unpredictability. The science of crystallization has evolved such that said differences in properties implies patentable distinctiveness between polymorphs.

Amount of direction/guidance & presence or absence of working examples

There is guidance for the preparation of salts in the specification (pages 12, 15, and 19); however, no direction or guidance is present in the instant specification for the preparation of solvates, esters, polymorphs, prodrugs, and metabolites for the compounds of formulae I, II, III or IV. Also, there are no working examples present in the disclosure for solvates, esters, polymorphs, prodrugs, and metabolites for the compounds of formulae I, II, III or IV. Therefore, one of skill in the art would be required to identify the correct solvent system and crystallization technique for each compound and, further, identify the similarities and differences between crystals and corresponding spectral data for each compound (polymorph) in order to determine what is being claimed.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include compounds of formulae I, II, III and IV, and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The quantity of experimentation necessary

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any solvates, esters, polymorphs, prodrugs or metabolites of a compound according to formulae I, II, III or IV as instantly claimed. The science of crystallization has evolved such that, without guidance or working examples for polymorphs in the specification, the claims lack enablement. This rejection can be overcome by deletion of the words: solvates, esters, polymorphs, prodrugs, and metabolites from **Claims 1, 7, 17 & 27.**

Claims 7 and 15 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compositions and a method of *treatment* for some diseases or disorders of the respiratory, urinary and gastrointestinal systems, (such as those listed in **Claims 11 & 15**: urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis), it does not reasonably provide enablement *for the treatment or for the prophylaxis* for any diseases or disorders of the respiratory, urinary and gastrointestinal systems. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention is compounds and compositions of formulae I, II, III or IV, the process for preparing these compounds, and methods of using these compounds.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for conditions such as urinary incontinence, lower urinary tract symptoms (LUTS), bronchial

asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis, but it does not mean that the same group of compounds and compositions may prevent said conditions.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for the *prophylaxis* of diseases or disorders of the respiratory, urinary and gastrointestinal systems as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of formulae I, II, III or IV to *treat* clinical conditions such as urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis is found on pages 34-36.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 7 & 15 are drawn to "the treatment or prophylaxis ..." Prophylaxis is commonly known to be synonymous with prevention. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Deleting the word "prophylaxis" in **Claims 7 & 15** and incorporating the limitations of **Claims 11 & 15** into **Claims 7 & 15** can overcome this rejection.

Claim Objections

Claims 1, 2, 7, 8 & 17 are objected to because of the following informalities: the language in the definition of **Y** is confusing. Examiner suggests adding a comma after the variable "methyl". Appropriate correction is required.

Claims 1-4, 7-10, 17 & 27 are objected to because of the following informalities: the language in the definition of **Q** is confusing. Examiner suggests adding commas after the variables "alkenyl" and "alkoxy". Appropriate correction is required.

Claims 4, 6, 10, 11, 16, 18, 19, 21, 22, 24, 25, 28, 29, 31, 32, 34, 35, 51 & 53 are objected to as being dependent upon a rejected base, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Allowable Subject Matter

Claim 5 is allowed.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: December 1, 2006